REMARKS

Claims 1-4, 12 and 13 are pending in the present application. Claims 5-11 have been cancelled without prejudice to or disclaimer of the subject matter contained therein. Claims 12 and 13 have withdrawn from consideration as being directed to non-elected subject matter.

Claims 5-11 have been cancelled, thus rendering the objection to claims 8-11 as being of improper dependent form, the provisional rejection of claims 8-11 on the ground of non-statutory obviousness-type double patenting, and the rejection of claims 5 and 8-10 as being anticipated, ***moot***.

Claims 5-11 have been cancelled for the sole reason of advancing prosecution. Applicants, by canceling or amending claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

No new matter has been added.

In view of the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding objections and rejections and allow all claims pending in this application.

I. At pages 3-6, paragraphs 2-4, of the Official Action, claims 8-11 have been provisionally rejected under on the ground of non-statutory obviousness-type double patenting.

Claims 5-11 have been canceled without prejudice or disclaimer, thus rendering these rejections moot as to claims 8-11. Accordingly, the Examiner is respectfully requested to withdraw these provisional rejections as to claims 8-11.

II. At page 6, paragraph 5, of the Official Action, claims 8-11 have been objected to as being of improper dependent form.

Claims 5-11 have been canceled without prejudice or disclaimer, thus rendering this objection moot as to claims 8-11. Accordingly, the Examiner is respectfully requested to withdraw this objection as to claims 8-11.

III. At page 9 of the Official Action, claims 1-11 have been rejected under 35 U.S.C. §103(a) over Bertrand et al. in view of Swingle et al.

The Official Action states that claims 1-11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bertrand et al. (FR 2804024; English language Derwent abstract) in view of Swingle et al. (1985).

As the basis of the rejection, the Official Action states in relevant part:

> Bertrand et al. disclose compositions for topical application to the skin (a transdermal formulation for external application) that comprise at least one non-steroidal anti-inflammatory active agent, at least one photo protective agent and an excipient or vehicle appropriate for external use (p 2, paragraph 3). The composition is intended to locally treat inflammation and/or joint pain (p 3). Preferred NSAIDS include ketoprofen (p 5, paragraph 2). Optional ingredients include antioxidants such as BHA and BHT (t-butyl p-cresol; p 7, paragraph 4). Examples comprising ketoprofen and BHA are presented (p 8-11).

> Bertrand et al. do not exemplify a composition comprising BHT and ketoprofen or disclose propyl gallate as a possible ingredient in the topical composition comprising ketoprofen.
>
> Swingle et al. disclose that both BHT and propyl gallate are phenolic antioxidants that exhibit *in vivo* anti-inflammatory activity (p 113, section IV and Table 1, p.114). The efficacy of these compounds as anti-inflammatory agents in different models of inflammation is presented in table 1 (p. 114).
>
> Swingle et al. teach that BHT and propyl gallate possess antioxidant activity but also act as non-steroidal anti-inflammatory agents. As such, these compounds would be useful for the treatment of inflammation. Bertrand et al. disclose a composition comprising ketoprofen and an antioxidant such as BHA or BHT that is also useful for the treatment of inflammation. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a composition comprising ketoprofen, BHT and propyl gallate as the prior art teaches each component as being useful for the same purpose. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) MPEP 2144.06
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> Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness has not been established in the present application. To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U.S. at_ ,82 USPA 2d 1385 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in

order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established in the present application because there is no apparent reason to prompt a person of ordinary skill in the art to combine the elements disclosed in the cited references in the way the presently pending claims do, as required by *KSR*, *supra*. Further, any *prima facie* case of obviousness, if established, is rebutted by the data presented in the Examples of the present specification which illustrate that the improvement achieved by the presently claimed subject matter is more than the predictable use of prior art elements.

Presently Pending Claims

Claim 1 is directed to a transdermal formulation for external application comprising a non-steroidal anti-inflammatory analgesic (ketoprofen, as elected) an alkyl ester of gallic acid (propyl gallate, as elected) and a phenolic radical scavenger having a branched-chain lower alkyl group (di-tert-butylhydroxytoluen, i.e. BHT, as elected).

Each of claims 2-4 directly depend from claim 1. Claim 2 recites that the phenolic radical scavenger is at least one member selected from the group consisting of BHT, BHA and thymol. Claim 3 recites that the alkyl ester of gallic acid is an ester of gallic acid and lower alcohol. Claim 4 recites the non-steroidal anti-inflammatory analgesic is at least one member selected from the group consisting of ketoprofen, tiaprofen, suprofen, tolmetin, carprofen, benoxaprofen, piroxicam, benzydamine, naproxen, diclofenac, ibuprofen, diflunisal and azapropazone.

The presently claimed transdermal formulation has a synergistic effect in reliably preventing photosensitivity that can be caused by the active ingredient, i.e., the non-steroidal anti-inflammatory analgesic, while at the same time the formulation exhibits anti-inflammatory analgesic effects. The photosensitivity/phototoxicity-reducing effect of the presently claimed transdermal formulation is synergistically enhanced when an alkyl ester of gallic acid is combined with a phenolic radical scavenger having a branched-chain lower alkyl group, where the effect is exerted more prominently in the skin. Accordingly, the presently claimed transdermal formulation can be used as a highly safe pharmaceutical. *See* paragraphs [0006] - [0009] of the present application as originally filed.

The synergistic effect achieved by the presently claimed transdermal formulation is demonstrated by Inventive Examples 4-5 and Comparative Examples 1-4 set forth in the present application. As confirmed by the "*in vivo* photosensitivity test" described in the examples, while Comparative Example 1 using 1.0% BHT shows 16% of Auricular edema inhibition (AEI) and Comparative Example 2 using 0.2% propyl gallate (PG) shows 21% of AEI, Inventive Example 4 using the combination of 1.0% BHT and 0.2% PG shows ***89%*** of AEI. In addition, while Comparative Example 3 using 0.5% BHA shows 24% of AEI and Comparative Example 4 using 0.2% PG shows 19% of AEI, Inventive Example 5 using the combination of 0.5% BHA and 0.2% PG shows ***84%*** of AEI.

Applicants submit that the synergistic effect achieved by the presently claimed subject matter results from the combined use of an alkyl ester of gallic acid (e.g., propyl gallate), with a phenolic radical scavenger having a branched-chain lower alkyl group (e.g., BHT or BHA), and is supported by the examples in the present specification.

Neither Bertrand et al. nor Swingle et al. Teach or Suggest all the Limitations of the Pending Claims

Bertrand et al. describe a topical formulation for application to the skin or mucosa which comprises (a) a non-steroidal anti-inflammatory agent (e.g., ketoprofen) as an active agent, (b) an ultraviolet radiation agent (e.g., 4-benzophenone) and (c) an inert excipient or carrier. Bertrand et al. further describe that component (b) prevents the chemical degradation of the active agent (a) which can degrade to form products that cause sensitization, irritation, phototoxicity and/or allergy. For example, Bertrand et al.

describe that component (b) prevents the light-induced degradation of ketoprofen to toxic/irritating 3-acetyl-benzophenone. Bertrand et al. further describe that the composition may optionally contain an antioxidant such as BHT, BHA, palmityl ascorbate or a tocopherol.

However, nowhere do Bertrand et al. teach or suggest the use of an alkyl ester of gallic acid, such as propyl gallate, as a possible component for the compositions described therein. Accordingly, Bertrand et al. fail to teach or suggest all of the elements of the presently pending claims.

Swingle et al. disclose the anti-inflammatory effect of some antioxidants including BHA, BHT, propyl gallate, DPPD and ethoxyquin. In particular, Table 1 at page 114 of the Swingle reference, describes the anti-inflammatory effects of BHT and propyl gallate, among others.

However, Swingle et al. do not teach or suggest a composition containing ***both*** BHT and propyl gallate, ether as an antioxidant or as an anti-inflammatory agent, or a composition containing a non-steroidal anti-inflammatory analgesic such as ketoprofen. Accordingly, Swingle et al. fail to teach all of the elements of the presently pending claims.

There is No Teaching or Suggestion that would Motivate a Person of Ordinary Skill in the Art to Combine Bertrand et al. with Swingle et al.

Applicants note that the Examiner states in the Official Action that it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare a composition comprising ketoprofen, BHT and propyl gallate as the prior art teaches

each component as being useful for the same purpose. The Examiner further states that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition to be used for the very same purpose, relying on *In re Kerkhoven*

In this regard, Applicants submit that to reject a claim directed to a combination of components as being obvious, it is not sufficient solely to show that each component is taught in prior art to be useful for the same purpose. To establish a *prima facie* case of obviousness for a combination of known elements, it is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR,* 550 U.S. at __, 82 USPQ2d at 1396.

Assuming *arguendo* that each of the components of present claim 1, namely a non-steroidal anti-inflammatory analgesic (ketoprofen), an alkyl ester of gallic acid (e.g., propyl gallate), and a phenolic radical scavenger having a branched-chain lower alkyl group (e.g., BHT), can be found in either Bertrand et al. or Swingle et al., nowhere do Bertrand et al. and/or Swingle et al. teach or suggest the combined use of a non-steroidal anti-inflammatory analgesic, an alkyl ester of gallic acid and a phenolic radical scavenger having a branched-chain lower alkyl group as presently claimed, let alone that the combined use of an alkyl ester of gallic acid (e.g., propyl gallate) and a phenolic radical scavenger having a branched-chain lower alkyl group (e.g., BHT) would exert a synergistic effect in inhibiting/reducing photosensitivity/phototoxicity of a transdermal formulation containing ketoprofen as an active ingredient.

As discussed above, Bertrand et al. teach the use of an ultraviolet radiation agent such as 4-benzophenone to prevent the chemical degradation of ketoprofen in a topical formulation. Accordingly, even though Bertrand et al. may describe a topical formulation containing ketoprofen and BHA in the examples, the skilled artisan reading the Bertrand reference would have no motivation to modify the topical formulation of Bertrand et al. by adding another antioxidant, e.g., propyl gallate.

Similarly, even though Swingle et al. may describe that both the antioxidants propyl gallate and BHT can have anti-inflammatory activity, Swingle et al. in no way suggest the use of both BHT and propyl gallate in a single composition, let alone identify or suggest the advantages of using both BHT and propyl gallate in a single composition. The skilled artisan, reading both the Bertrand et al. and Swingle et al. references, would have no motivation to combine BHT and propyl gallate in a single composition. Accordingly, a prima facie case of obviousness has not been established in the present application.

The synergistic effect of the present claims are unpredictable from the teachings of Bertrand et al. and Swingle et al.

To establish the obviousness of a combination, it must be determined whether the improvement is more than the predictable use of prior art elements according to their established functions. *KSR,* 550 U.S. at ___, 82 USPQ2d at 1395. Combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966). Further, as set forth in

M.P.E.P. §2144.08, rebuttal evidence [against a *prima facie* obviousness] may include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillion*, 919 F.2d at 692-93, 16 USPQ2d at 1901.

In the present application, the synergistic effect of inhibiting or reducing the photosensitivity and/or phototoxicity of the active agent of the claimed transdermal formulation, is unexpected and is significantly greater than the inhibition/reduction that would be predictable and/or expected. The predictable use of BHT as disclosed in the Bertrand et al. reference is as an antioxidant and the predictable use of propyl gallate as disclosed in the Swingle et al. reference is also as an antioxidant that may additionally exert anti-inflammatory activity. Accordingly, the predictable use of BHT and propyl gallate, if combined, would be the same, namely as an antioxidant having a merely additive effect.

The unexpected synergistic effect achieved by the presently claimed transdermal formulation, i.e., the inhibition or reduction of photosensitivity/phototoxicity caused by the active agent of the formulation, is ***not predictable*** from Bertrand et al. and Swingle et al., taken alone or together. Rather, the skilled artisan, in view of Bertrand et al. and Swingle et al., would expect that any inhibition/reduction that would be achieved by the combined use of the antioxidants BHT or propyl gallate, would be ***merely additive***. The presently claimed transdermal formulation exhibits unexpectedly superior inhibition/reduction of photosensitivity/phototoxicity, as compared to the

inhibition/reduction achieved by either BHT or propyl gallate alone, as well as compared to the inhibition/reduction that would be expected from their combined use.

Moreover, as can be seen from Inventive Examples 4-5 and Comparative Examples 1-4, the presently claimed combination of a phenolic radical scavenger, e.g., BHT, and an alkyl ester of gallic acid, e.g., PG, achieves unexpectedly superior Auricular edema inhibition (AEI) as compared to the AEI achieved by either antioxidant alone or the AEI that would be expected from their combined use. For example, the use of BHT alone results in 16% AEI and the use of PG alone results in 21% AEI. Thus, assuming *arguendo* motivation to use BHT and PG together, the skilled artisan would expect that their combined use would result in about 37% AEI. In fact, the combined use of BHT and PG, as presently claimed, unexpectedly results in 89% AEI. *See* Inventive Example 4 and Comparative Examples 1 and 2. Likewise, Comparative Example 3 illustrates the use of BHT alone which results in 24% AEI and Comparative Example 4 illustrates the use of PG alone which results in 19% AEI. Thus, assuming *arguendo* motivation to use BHT and PG together, the skilled artisan would expect that their combined use would result in about 43% AEI. In fact, the combined use of BHT and PG, as presently claimed, unexpectedly results in 84% AEI. *See* Inventive Example 5 and Comparative Examples 3 and 4.

Accordingly, the unexpectedly superior results achieved by the presently claimed subject matter, i.e., the unpredictable synergistic inhibition/reduction evidenced by the

examples set forth in the present specification, clearly establishes that the claimed combination of ingredients would not have been obvious in view of any alleged known use of these ingredients individually.

As such, a *prima facie* case of obviousness, if established, is rebutted by the unexpectedly superior inhibition/reduction achieved by the presently claimed subject matter.

In view of the foregoing, it is submitted that nothing in Bertrand et al. or Swingle et al., taken alone or together, renders the claimed invention obvious within the meaning of 35 U.S.C. §103(a). Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

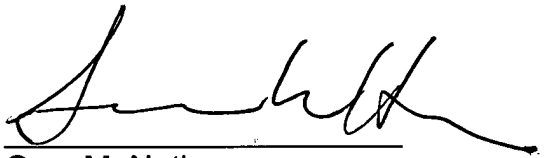
CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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Gary M. Nath
Registration No. 26,965
Susanne M. Hopkins
Registration No. 33,247
Customer No. 20529

THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314
Phone: (703)548-6284

GMN/SMH\MSK:oa.doc